Remarks

1. Status of the Claims

Claims 1-77 were under consideration in the office action. Pursuant to a telephonic election of Group 1, claims 1-27, 32-38, 69 and 77 were examined.

The status of the examined claims is not entirely clear from the office action. The office action summary states that claims 1-6, 8-13, 15, 16, 18, 19, 32-38 and 77 are **allowed** but that claims 7, 14, 17, 20-27, and 69 are objected to. However, the office action contains **rejections** of claims 1-6, 8-13, 15, 16, 18, 19, 33-38 and 77, and states that claims 7, 14, 17, 20-27, and 69 are allowable but objected to for depending upon a rejected base claim.

The applicants assume that the office action summary should have stated claims 1-6, 8-13, 15, 16, 18, 19, 33-38 and 77 were rejected since the office action discusses grounds for rejecting these claims.

The applicants respectfully point out that the office action appears incomplete as to claims 32 and 36. No discussion of the status of claim 32 or 36 appears in the office action other than in the office action summary, where these claims were stated to be allowed. The examiner is respectfully requested in the next office action to clarify the status of claims 32 and 36. If the examiner intended to allow claim 32 and 36, the examiner is respectfully requested to make this clear. If the examiner intended to reject claim 32 and 36, the examiner is respectfully requested to set forth the reasons for the rejection.

2. Explanation of the Amendments

Claim 1 is amended to delete the option for B to be unsubstituted aryl. The proviso requiring B to be substituted when A and B are both phenyl is deleted as being superfluous in view of this amendment (since the amendment requires that if B is phenyl, it must be substituted, and therefore at least one of A and B would necessarily be substituted). The amendment is supported by the recitation in original claim 1 that B may be substituted aryl.

In claims 1, 12, 16, 19, 74, 75 and 76 the term "conformation", referring to designations of stereochemistry, is corrected to "configuration".

In claims 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 18, 19, 20, 21, 22, 23, 24 and 25, the expressions "or a salt thereof" or "or a salt of such a compound" are added to make clear that the claims are intended to encompass salt forms of the compound. This amendment is supported by the specification at p. 74 line 9 where it is stated that the compounds of the invention may take the form of salts. It is applicants' position that the original claims encompassed salt forms of the compounds (since the specification expressly stated that the salts are regarded as a "form" of the compounds, salts were therefore encompassed by the claims to the "compounds"), and the amendments are made only to make this even more clear. Similarly, claim 27 amended to make clear that a pharmaceutical composition may comprise the compounds of the invention in a pharmaceutically acceptable salt form. The specification makes clear that the compounds of the invention may take the form of salts and pharmaceutically acceptable salts (see, e.g., p. 25 line 15 and the discussion beginning at p. 74 line 9). The person skilled in the art would understand that a salt form used in a pharmaceutical composition should be pharmaceutically acceptable. Similarly, claims 32, 37, 40, 47, 49, 51, 52, 53, 54, 55, 59, 60, 61, 62, 66, 67 and 68 have been amended to make clear that a pharmaceutically acceptable salt form of the compounds of the invention may be used in the methods of treatment claimed therein.

Claim 4 has also been amended to correct $-(C_1\text{-}C_3)$alkylene-$N^+(C_1\text{-}C_3)_3$ to $-(C_1\text{-}C_3)$alkylene-$N^+((C_1\text{-}C_3)\underline{\text{alkyl}})_3$. The person skilled in the art would immediately recognize that $(C_1\text{-}C_3)$ was clearly intended to refer to a trialkylammonium moiety as an unfunctionalized $(C_1\text{-}C_3)$ moiety, and that identification of the functional groups involved would have been required if any other type of $(C_1\text{-}C_3)$ moiety were intended.

In claims 7 and 17, "and salts thereof" is deleted, since these claims are directed to compounds of Formula **I** that would not have ionizable functional groups, and would not therefore exist in salt forms.

Claim 4 has been amended to conform to the amendment made to claim 1, whereby the independent definitions of A^1 and B^1 as aryl or heteroaryl have been separately set forth and y

limited to 1, 2, 3, 4, or 5 when B^1 is aryl. This amendment is supported by the recitation in original claim 1 that B may be substituted aryl (i.e. aryl having at least one substituent). In addition, the limitation that x and y should not exceed the number of substitutable hydrogen atoms has been reworded. The person skilled in the art would readily understand the meaning of the limitation as originally worded, i.e. to prevent the value of x or y to exceed the number of substitutable positions of an aromatic ring (A or B). For example, a phenyl group has 5-substitutable positions, i.e. positions that are occupied by hydrogen when the phenyl ring is unsubstituted and which may be substituted by other substituents. Similarly a 2-pyridyl group has four substitutable positions, the unsubstituted 2-pyridyl group having four hydrogen atoms available for substitution by other substituents. Applicants are of the opinion that the rewording to refer to substitutable "positions" conveys the meaning more clearly and unambiguously. Applicants have also replaced the reference to x and y being attached to the rings with R^a and R^b. Although the meaning of this limitation in claim 4 would have been clear to the person skilled in the art, it is more correct to state that R^a and R^b (the substituents) are attached to rings A and B rather than x and y, since x and y designate the number of substituents rather than the substituents themselves.

Claims 11, 18, and 59 have been amended to correct minor grammatical errors.

Claims 13, 15 and 18 have been amended to delete the option y=0 (to conform to the amendment of claim 1 deleting the option that B may be unsubstituted).

Claims 6 and 21 have been amended to depend from claim 4.

Claim 33 has been amended to correct typographical errors.

Claims 69, 72 74 and 76 have been amended to delete the option that B may be unsubstituted aryl to conform to the amendment made to claim 1.

The amendments to the specification have been made to correct minor typographical errors and/or make amendments conforming to the amendments made to the claims as described above.

3. Response to the Restriction Requirement

The prior restriction requirement was withdrawn and substituted by a new restriction requirement between Groups 1 to 11, characterized by the examiner as:

> **Group 1.** Claims 1-27, 32-38, 69 and 77, drawn to compounds, wherein n is 1, their composition, process for making the compounds and method of using the compounds, classified in class 514, subclass 355+.
>
> **Group 2**. Claims 1-27, 32-38, 69 and 77, drawn to compounds, wherein n is 0, their composition, process for making the compounds and method of using the compounds, classified in class 514, subclass 355+.
>
> **Group 3**. Claims 27-31 and 39 drawn to a conjugate, its composition and method of treatment, classified in class 514, subclass 355+.
>
> **Group 4**. Claims 40-54 drawn to a method of reducing or eliminating the effects of ionizing radiation, classified in class 514, subclass 355+.
>
> **Group 5**. Claims 55-68 drawn to a method of protecting an individual from cytotoxic side effects, classified in class 514, subclass 339+.
>
> **Group 6**. Claims 70 and 75 drawn to a compound of formula II and a process of making the same, classified in class 564, subclass 355+.
>
> **Group 7**. Claim 71 drawn to a compound of formula II and a process of making the same, classified in class 546, subclass 315+.
>
> **Group 8.** Claim 72 drawn to a process of making the compound of formula Iz, classified in class 568, subclass 63+.
>
> **Group 9.** Claim 73 drawn to a process of making the compound of formula IV and a process of making the same, classified in class 546, subclass 315+.
>
> **Group 10**. Claim 74 drawn to a process of making the compound of formula V and a process of making the same, classified in class 546, subclass 315+.
>
> **Group 11**. Claim 76 drawn to compound of formula IV, classified in class 546, subclass 315+.

Applicants affirm the telephonic election of Group 1 *with traverse.* Applicants set forth below detailed reasons for traversing the restriction requirement.

In making the restriction requirement, the examiner states that unity is lacking because: "[t]here is no special technical feature, which unites the groups"; (2) "even if there were a special technical feature there must be unity of invention also"; and (3) "groups 1-11 together do not

meet the requirement of unity of invention as given ... in [subparagraphs] (1)-(5) [of 37 C.F.R. § 1.475(b)]."

(a) The Examiner Used Incorrect Legal Standards in Making the Restriction Requirement

"Unity of invention (not restriction) practice is applicable in ... national stage applications submitted under 35 U.S.C. 371." MPEP 1893.03(d). Unity of invention must be determined under the provisions of the P.C.T. in a national stage application filed under 35 U.S.C. § 371. *Caterpillar Tractor Co. v. Com'r Pat. & Trademarks*, 650 F. Supp. 218 (E.D. Va. 1986). The legal standards applicable to making a restriction requirement in an application filed under 35 U.S.C. § 371 are therefore those set forth for determining unity of invention under the P.C.T., as given in the P.C.T. itself and the P.C.T. rules (specifically Rule 13). Authoritative guidance on the application of the P.C.T. and the P.C.T. rules is provided in the Administrative Instructions under the P.C.T., as well as the P.C.T. International Search and Preliminary Examination Guidelines.

Under the standard for unity of invention applicable in a national stage applications submitted under 35 U.S.C. § 371, the presence of a special technical feature linking the claims satisfies the unity of invention requirement. As 37 C.F.R. § 1.475(a) states, "the requirement of unity of invention *shall be fulfilled ... when there is a technical relationship* among those inventions *involving one or more of the same or corresponding special technical features*" (emphasis added). The presence of a special technical feature linking the claims thus defines the unity of invention standard.

Unity of invention is thus not a separate requirement from the presence of special technical features, and the examples quoted in subparagraphs (1)-(5) of 37 C.F.R. § 1.475(b) do not define unity of invention. 37 C.F.R. § 1.475(b) states that "a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the ... combinations of categories" defined in subparagraphs (1)-(5). While 37 C.F.R. § 1.475(b) does present situations where the unity of invention requirement "will be considered" to be met, the regulation does *not* state that unity of invention is *only* satisfied in the situations presented in subparagraphs (1)-(5). Rather, a

definition of "unity of invention" is given in 37 C.F.R. § 1.475(a), and under that definition the "unity of invention" requirement is satisfied when there is one or more special technical features linking the claims.

In making the restriction requirement, the examiner misstated the legal standard for unity of invention in at least two ways.

The examiner stated that unity was lacking because: (1) "[t]here is no special technical feature, which unites the groups"; (2) "even if there were a special technical feature there must be unity of invention also"; and (3) "groups 1-16 together do not meet the requirement of unity of invention as given ... in [subparagraphs] (1)-(5) [of 37 C.F.R. § 1.475(b)]."

The examiner first erred by incorrectly stating that there are two separate requirements for unity of invention (a special technical feature *plus* unity of invention). As pointed out above, the presence of a special technical feature defines unity of invention, so the presence of a special technical feature and unity of invention are not separate requirements.

The examiner secondly erred by incorrectly stating that the requirements for the separate unity of invention requirement are "given in" 37 C.F.R. § 1.475(b). As pointed out above, while Rule 1.475(b) does present situations where the unity of invention requirement "will be considered" to be met, the rule does *not* purport to define unity of invention or provide an exclusive list of when situations where unity of invention is satisfied.

Since the examiner used incorrect legal standards in making the restriction requirement, the examiner reached an erroneous conclusion in finding eleven separate inventions in applicants' application.

(b) The Examiner Should Have Found Unity of Invention Among the Claims the Application.

The claims of the present application are clearly directed to a single general inventive concept, namely the novel styryl sulfoxides of Formula **I** as described in claim 1, useful in treating proliferative disorders, including cancer.

(i) The Applicable Legal Standards

Unity of invention under the P.C.T. is the standard applicable to making a restriction requirement under 35 U.S.C. § 371. *See Caterpillar Tractor Co. v. Com'r Pat. & Trademarks*, 650 F. Supp. 218 (E.D. Va. 1986). The standard for unity of invention is set forth in P.C.T. Rule 13, which states that:

> "the requirement of unity of invention ... shall be fulfilled ... when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

P.C.T. Rule 13.2. Thus unity of invention is satisfied when there is a special technical feature linking the claims.

Authoritative guidelines for the determination of whether there is unity of invention in specific situations are provided in the Annex B to the Administrative Instructions under the P.C.T. (the "Administrative Instructions") and also in Chapter 10 of the P.C.T. International Search and Preliminary Examination Guidelines (the "Preliminary Examination Guidelines"). Particular standards set forth in these guidelines that are relevant to unity of invention in the present application are discussed in greater detail below.

First, where there is unity of invention within and among independent claims, there is also unity of invention among dependent claims. The Administrative Instructions explain that unity of invention should be considered first in relation to the independent claims. Then, "[i]f the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims" Administrative Instructions under the P.C.T. Annex B, para. (c)(i).

Second, there is unity of invention as between claims to a product, and claims to methods of making and using the product. The Administrative Instructions explain that the standard for unity of invention under Rule 13.2 should be construed as permitting "in addition to an independent claim for a given product, an independent claim for a process specially adapted for

the manufacture of the said product, and an independent claim for a use of the said product." Administrative Instructions under the P.C.T. Annex B, para. (c)(i).

Third, unity of invention exists in certain circumstances as between claims to a product and claims to intermediates used in the synthesis of the product. Specifically, the Administrative Instructions state that:

> (ii) Unity of invention shall be considered to be present in the context of intermediate and final products where the following two conditions are fulfilled:
>
> > (A) the intermediate and final products have the same essential structural element, in that:
> >
> > > (1) the basic chemical structures of the intermediate and final products are the same, or
> > >
> > > (2) the chemical structures of the two products are technically closely interrelated, the intermediate incorporating an essential structural element into the final product, and
> >
> > (B) the intermediate and final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element.

Administrative Instructions under the P.C.T., Annex B, para. (g)(ii). Further, the presence in an application of claims to different intermediate products used in different processes for the preparation of the final product is not inconsistent with unity of invention among the claims where the claimed intermediates have the same essential structural element. Administrative Instructions under the P.C.T., Annex B, para. (g)(iv). Unity of invention is also not defeated by the possibility that the intermediates may have other effects or activities beyond ability to produce final products. Administrative Instructions under the P.C.T., Annex B, para. (h).

Fourth, it is to be noted that unity of invention is to be determined according to the presence or otherwise of a special technical feature linking the claims, and not by the way the invention is claimed. P.C.T. Rule 13.2 makes clear that unity of invention is determined according to whether there is a special technical feature linking the claims. This determination is not to be affected by the manner in which the invention is claimed so long as the requirements for unity of invention are otherwise satisfied. *See* P.C.T. Rule 13.3.

Finally, the Administrative Instructions establish that when a series of chemical compounds is defined in a claim using so-called "Markush practice" enumerating alternative elements, "[t]he fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention." Administrative Instructions under the P.C.T. Annex B, para. (f)(iv). Unity of invention is satisfied when a significant structural element is shared by all of the alternatives. The significant structural element may be a single component or a combination of individual structural elements linked together. Administrative Instructions under the P.C.T. Annex B, para. (f).

(ii) Description of the Special Technical Features that Link the Claims and How the Special Technical Feature Links the Claims

The novel compounds of Formula **I** are a feature occurring in each of claims 1-77 which make a contribution over the prior art, and are thus clearly a special technical feature linking claims 1-77.

Claims 1-4, 6-26 and 77 are directed to compounds of Formula **I** and various embodiments thereof.

Claims 69-73 are directed to chemical *processes of making* compounds of Formula **I** and the various embodiments thereof. The examiner mischaracterizes claims 70 and 71 as being drawn to a process for preparing a compound of Formula **II**. These claims are dependent from claim 69 and therefore clearly directed to a process of making compounds of Formula **I**. The compound of Formula **Iz** prepared in claim 72 is an embodiment of the compound of Formula **I** (as claimed in claim 2) and is therefore clearly directed to a process of making compounds of Formula **I**. The examiner mischaracterizes claim 73 as being drawn to a process of preparing a compound of Formula **IV**. However, this claim depends from claim 72 and is therefore clearly directed to a process of making compounds of Formula **I**.

Claims 28-30 are directed to conjugates in which the compound of Formula **I** is conjugated to an antibody.

Claim 27 is directed to a pharmaceutical composition comprising the compounds of Formula **I**.

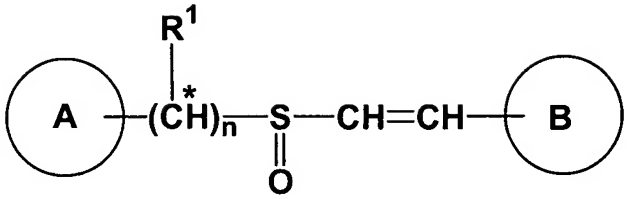
Claim 31 is directed to pharmaceutical compositions comprising the antibody conjugates of the compounds of Formula **I**.

Claims 32-38, 40-68, and 74 are all directed to methods of using the compounds of Formula **I**. Claims 32-36 are directed to methods of treating proliferative disorders by administering the compounds of Formula **I**. Claims 37-38 are directed to methods of treating cancer by inducing apoptosis of tumor cells by administering the compounds of Formula **I**. Claims 40-54 are directed to methods of using the compounds of Formula I for protecting individuals or cells from the effects of radiation. Claims 55-68 are directed to methods of using the compounds of Formula **I** for protecting against cytotoxicity. Claim 74 is directed to a method of using compounds of Formula **I** as a starting material for the synthesis of compounds according to Formula **V**.

Claims 39 is directed methods of using the antibody conjugates of the compounds of Formula **I**, specifically by to a method of treating cancer by administering the conjugate.

The compounds of Formula **I** and the structural features present in the compounds of Formula **I** are clearly unifying special technical features that link the claims in a single inventive concept.

The compounds of Formula **I** are clearly a unifying technical feature of Groups 1 and 2 (claims 1-27, 32-38, 69 and 77 wherein 1 n is either 1 or 0 respectively). The examiner does not appear to allege otherwise other than by drawing a distinction between the compounds wherein n is 1 (Group 1), and those wherein n is 0 (Group 2). Restriction is clearly improper as between Groups 1 and 2. These claims have in common the essential structural elements of the compounds of Formula **I**, namely the combination of Ring A with a vinylic sulfoxide moiety terminated by Ring B, wherein the Ring A and vinylic sulfoxide are linked closely to each other. The fact that the compounds are closely related structurally would appear to be established by the fact that the claims have been identically classified by the examiner.



I

The distinction drawn by the examiner between Groups 1 and 2 as to the value of n in the definition of the compounds of Formula **I** is insufficient to establish lack of unity. As pointed out above, the Administrative Instructions under the P.C.T. explain that "[t]he fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention." Administrative Instructions under the P.C.T. Annex B, para. (f)(iv). Unity of invention is satisfied when a significant structural element is shared by all of the alternatives. The significant structural element may be a single component or a combination of individual structural elements linked together. Administrative Instructions under the P.C.T. Annex B, para. (f).

Here the compounds of Formula **I**, regardless of whether n is 1 or 0 (Groups 1 and 2), meet the requirements for unity of invention because a significant structural element is shared by all the compounds of Formula **I**. The significant structural element is defined by the combination of Ring A with a vinylic sulfoxide moiety terminated by Ring B, wherein the Ring A and vinylic sulfoxide are linked closely to each other (a separation of no more than two bonds). The compounds of Formula **I** all share these structural features regardless of whether Ring A is directly connected to he sulfoxide (when n=0) or connected via a one carbon linkage. It is not significant for the purposes unity of invention that n may be one or zero such that the (CHR^1) moiety "interrupts" the linkage between ring A and the sulfoxide group: the significant structural element shared by the alternatives to establish unity of invention may be *a combination of individual structural elements linked together*. Administrative Instructions under the P.C.T. Annex B, para. (f).

The restriction requirement made is also clearly improper insofar as restriction has been required between Groups 1 and 2 with Groups 4 and 5. The claims of Group 1, 4 and 5 relate to novel compounds of Formula **I** (Groups 1 and 2: the compounds of Formula **I** in claim 1) and two methods of use of those compounds (Group 4 – method of eliminating effects of ionizing

radiation; and Group 5 – method of protection from ionizing radiation). Claims for products and for uses of the product are explicitly recognized as satisfying the unity of invention standard in the Administrative Instructions for determining unity of invention under the P.C.T. (Administrative Instructions under the P.C.T. Annex B, para. (e)(i)), as well as by the MPEP 1850(III)(A), and the Patent Office Rules (37 C.F.R. § 1.475(b)(3)). The compounds of Formula **I** are clearly a special technical feature linking Groups 1 and 2 on the one hand and Groups 4 and 5 on the other hand.

The restriction as between Groups 1 and 2 and 4 and 5 is also improper to the extent it ignores claim dependencies. All of the claims of Groups 4 and 5 depend directly or indirectly from claim 1 (Group 1). Claim dependency is a basis for unity of invention. *See* Administrative Instructions under the P.C.T., Annex B, para. (c)(i) ("If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims"). Therefore there must be unity of invention between Groups 1 and 2 and 4 and 5.

Unity of invention also exists as regard to Group 3, since the compounds of Formula **I**, as defined by claim 1, again are a unifying special technical feature. The structure of the antibody conjugates of Group 3 comprises a compound of claim 1 linked to an antibody. The claims to the antibody conjugates of Group 3 are clearly part of the same general inventive concept as the claims to the compounds per se of Groups 1 and 2, and their medical use. The antibody conjugates connect the compounds of Formula **I** (claim 1) to an antibody in order to target the delivery of the compound of Formula **I** to the appropriate site in the body, but, nevertheless, the useful therapeutic utility of the conjugate arises because of the incorporation of the compound of Formula **I** as an essential structural element which imparts the desired activity. The Formula **I** structure is therefore a technical feature unifying the antibody conjugates of Group 3 with the compounds of Groups 1 and 2.

The restriction requirement is also improper to the extent it ignores the dependency of the Group 3 claims on the claims of Group 1 and 2. Each of the claims of Group 3 depends directly or indirectly from claim 1 and 2.

The restriction as it relates to Groups 6 and 7 is also improper. Group 6 comprises claims 70 and 75. Group 7 comprises claim 71.

Contrary to the examiner's assertion, claim 70 is not directed to the intermediate of Formula **II** but rather is directed to a process for preparing compounds according to Formula **I** having *E* stereochemistry of the double bond (i.e. compounds of Formula **Ie** as claimed in claim 3). This can be appreciated by noting that claim 70 depends from claim 69. Similarly, claim 71 depends from claim 70 and is also therefore also directed to a process for preparing compounds according to Formula **I** having E-stereochemistry. Thus, clearly, the compounds according to Formula **I** are a special technical feature linking claim 70 of Group 6 and claim 71 of Group 7 since these claims claim methods of making compounds according to Formula **I**.

Furthermore, the restriction as to claim 70 (Group 5) and claim 71 (Group 6) is improper in that both claims depend, directly or indirectly, from claim 69, which itself is grouped in Group **I**. Claims 70 and 71 further limit the process as defined in claim 69 by reciting further steps. As indicated above, claim dependency is a basis for unity of invention. *See* Administrative Instructions under the P.C.T., Annex B, para. (c)(i).

The restriction requirement is also improper as to Groups 8 (claim 72) and 9 (claim 73). Claim 72 is directed to a method for the preparation of the compounds of Formula **Iz** (claim 2), i.e. compounds of Formula **I** having *Z* stereochemistry. Thus, compounds of Formula **I** are a special technical feature linking claims 72 and 73 with claim 1. Claim 73 depends from claim 72, and recites the upstream step by which the starting material of claim 72 (the Formula **IV** compound) is made.

Unity of invention is present as between Groups 1 and 2 and Groups 8 (claim 72) and 9 (claim 73) in that the process of claim 72 defines a method for making the compounds of claim 2. As indicated above, unity is present as between a product and a method of its production. Unity of invention is present also as to claim 73, since that claim depends from claim 72, and recites a further feature thereof, namely a preparation method for making the starting material of the claim 72 method, i.e. the Formula **IV** compounds.

Unity of invention as between Group 1 and 2 and Groups 7 (claim 72) and 8 (claim 73) is also apparent from claim dependency. Claims 72 and 73 depend directly or indirectly from claim 2, which is grouped in Groups 1 and 2. Thus, because of claim dependency, unity of invention is present between Group 1 and 2 and Groups 7 and 8. *See* Administrative Instructions under the P.C.T., Annex B, para. (c)(i).

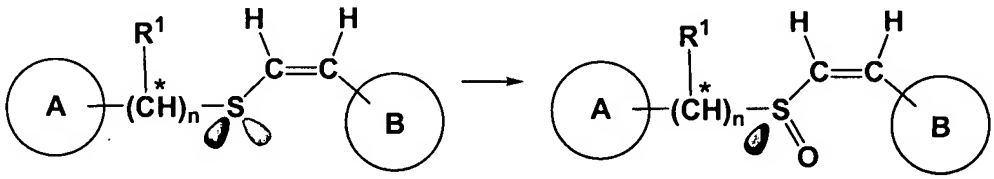
The restriction requirement is improper as it relates to Group 10. Unity of invention is present as between Group 1 and Group 10 (claim 74). Claim 74 defines a *method of using* the sulfoxides of Formula **I** (claim 1) in the production of the corresponding sulfones. Claim 1 and claim 74 are therefore related as product and method of use. Claims for products and uses thereof satisfy the unity of invention standard (Administrative Instructions under the P.C.T., Annex B, para. (e)(i)), as well as by the MPEP 1850(III)(A), and the Patent Office Rules (37 C.F.R. § 1.475(b)(3)). Thus, the compounds of Formula **I** are clearly a special technical feature linking Group 1 and 2 on the one hand and Groups 10 on the other hand.

The restriction requirement is improper as it relates to claim 75 of Group 6, directed to an intermediate compound of Formula **II** and Group 11 (claim 76) directed to an intermediate compound of Formula **IV**. These claims are directed to intermediates that are useful in the synthesis of compounds of Formula **I**. As such, the claims to the intermediates meet the requirements for unity of invention with the claims to the compounds of Formula **I**, which is satisfied when:

> (A) the intermediate and final products have the same essential structural element, in that:
>
> > (1) the basic chemical structures of the intermediate and final products are the same, or
> >
> > (2) the chemical structures of the two products are technically closely interrelated, the intermediate incorporating an essential structural element into the final product, and
>
> (B) the intermediate and final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element.

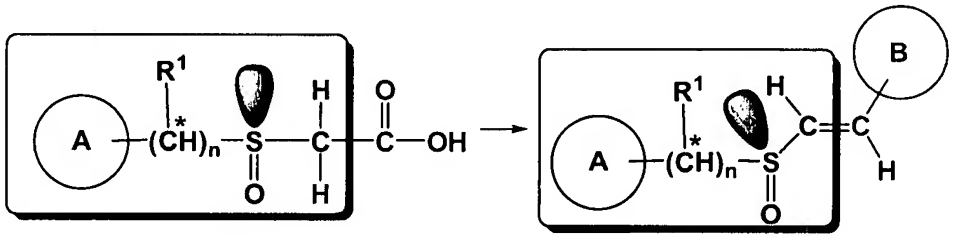
Administrative Instructions under the P.C.T., Annex B, para. (g)(ii).

The requirement of technical close interrelationship between the intermediates of claims 75 and 76 and the compounds of Formula **I** is satisfied because the intermediate of claim 76 incorporates the highlighted essential structural element into the final product:



IV **Iz**

while the intermediate of claim 75 incorporates the following essential structural element into the final product.



II **Ie**

In the above diagrams, the orbitals attached to sulfur depict the lone pairs of electrons of the sulfide and sulfoxide groups. The examiner will note that the highlighted structural element in Formula **II** and incorporated by the intermediate of Formula **II** into the final product is also present in compound **IV** and incorporated by the intermediate of Formula **IV** into the final product.

The requirement of technical interrelationship in that the final compound is manufactured directly from the intermediate is met for both intermediates since both may be converted directly to the compounds of Formula **I**. The intermediate of claim 75 may be converted to a compound of Formula **I** by a condensation reaction with an aldehyde as described in the specification on pp. 40-41, while the intermediate of claim 76 may be converted to a compound of Formula **I** by a condensation reaction with an aldehyde as described in the specification on pp. 40-41.

(iii) Conclusion: Claims 1-77 Satisfy the Unity of Invention Standard under the P.C.T.

Unity of invention under the P.C.T. is the standard applicable to making a restriction requirement under 35 U.S.C. § 371. *See Caterpillar Tractor Co. v. Com'r Pat. & Trademarks*, 650 F. Supp. 218 (E.D. Va. 1986).

Claims 1-77 satisfy the unity of invention standard and therefore the examiner, upon reconsideration, should find that the requirement of restriction requirement was made improperly. Unity of invention is satisfied when there is a special technical feature linking the claims. P.C.T. Rule 13.2. Applicants' remarks demonstrate that the novel compounds of Formula **I** are a special technical features that link each of claims 1-77. The claims are all directed to a single general inventive concept, namely the compounds of Formula **I**. More specifically, all the claims are directed to the compounds of Formula **I**, methods of treatment using them, processes for making them, and intermediates that are useful in making them.

(c) To the Extent that Lack of Unity Exists as to Any of the Pending Claims, Applicants Are Entitled to Rejoinder of All Claims Sharing Unity of Invention with Applicants' Elected Invention.

Unity of invention under the P.C.T. is the standard applicable to making a restriction requirement under 35 U.S.C. § 371. *See Caterpillar Tractor Co. v. Com'r Pat. & Trademarks*, 650 F. Supp. 218 (E.D. Va. 1986).

Under unity of invention practice, an applicant has the "right to include in a single application ... those inventions which are so linked as to form a single general inventive concept." See P.C.T. Rule 13.1 and also MPEP 1893.03(d). The requisite unity of invention is present where there are one or more special technical features linking the claims. P.C.T. Rule 13.2.

Therefore, restriction in an application filed under 35 U.S.C. § 371 may not properly be required between groups of claims that are "linked as to form a single general inventive concept", i.e. groups of claims that have a linking special technical feature. Upon a finding of lack of unity of invention as to all the claims, the examiner is not thereby given "carte blanche" under the P.C.T. to divide applicants' claims as he sees fit. Rather, since the applicants have the

"right to include in a single application ... those inventions which are so linked as to form a single general inventive concept", applicants are entitled to retain in the application those claims that share a special technical feature (i.e. unity of invention) with the elected invention and each other.

Even if the examiner, upon reconsideration, finds that lack of unity exists as to some of the claims of the invention, the examiner is respectfully nevertheless respectfully requested to consider applicants detailed arguments presented above as to the special technical features present among the claims. The examiner is respectfully requested to rejoin any claims found to share one or more special technical features with the applicants' elected invention so as to permit the applicants to retain in the application all "those inventions which are so linked as to form a single general inventive concept."

(d) Conclusion

Applicants respectfully submit that the foregoing demonstrates that the examiner failed to apply the proper legal standards in making and reconsidering the restriction requirement.

Applicants respectfully submit that the restriction requirement was improper and that the examiner should have found unity of invention to exist as to all of claims 1-77.

4. Response to the Claim Rejections.

(a) Rejection of Claims 33-35, 37 and 38 under 35 U.S.C. § 112 First Paragraph Enablement Requirement.

The examiner has rejected claims 33-35, 37 and 38 under 35 U.S.C. § 112 as allegedly containing subject matter which is not described in the specification in such a way as to enable a person skilled in the art to make and or use the invention. The applicants respectfully traverse.

The examiner acknowledges that the claims are enabled for certain cancers, specifically breast, prostate, lung, and colorectal cancers but disputes enablement as to other proliferative diseases.

The examiner concludes on the basis of several factual assertions that the claims are insufficiently enabled. The examiner claims that the asserted utilities which the examiner is of the opinion are insufficiently enabled are "speculative", and "goes beyond what is known in the art", and that the rejected insufficient guidance for the claimed method of treatment. As grounds for rejection, the examiner includes the observation that there is "no known treatment with the claimed compound", and that there is there is "no known success for the treatment of" the particular diseases "with the claimed compounds". The examiner asserts that "no animal models exist" for the treatment of the diseases for which methods of treatment are claimed and "it will be necessary for an ordinary skilled artisan to have clinical data in order to practice the claimed invention."

Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. *See In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971). The initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *See In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984).

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The factors to be considered in determining whether any necessary experimentation is "undue" include the factors described in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988),

namely: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) The level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The examiner's analysis is couched in terms of an analysis under the *Wands* factors. The gist of the examiner's grounds of rejection appears to be the contention that the treatment of cancer and other proliferative disorders with the claimed compounds is novel, and that the person skilled in the art would require clinical data in order to practice the invention. The examiner asserts (without presenting any evidence whatsoever) that the treatment of cancer and proliferative diseases is a "speculative field" and that therefore that the applicant has provided "no guidance" and no examples of treating cancer and proliferative diseases. The examiner asserts that the person of skill in the art would not be able to practice the invention without having clinical data.

The applicants respectfully point out that given that the examiner has not presented any evidence to support the factual assertions made by the examiner concerning the state of the art, the examiner has not met the evidentiary burden required to overcome the presumption that applicants have met the enablement requirement is met. The examiner has made various assertions concerning the state of the art, but no *evidence* has been produced, and no reasons have been presented why the person skilled in the art would question objectively whether the person skilled in the art would be able to make and use the invention recited in the rejected claims.

It is moreover respectfully submitted that the examiner overstates both the level of unpredictability and the level of validation needed in order to satisfy the enablement requirement of 35 U.S.C. § 112 first paragraph. At the same time the examiner underestimates the level of skill and state of knowledge in the art, as well as the amount of experimentation typically involved in drug development. All these factors show that the quantity of experimentation required to practice the claimed invention would be far from undue. The applicants are gratified by the examiner's observations that the claimed methods of treatment using the compounds of

the invention are not known in the art. However, given the statutory requirement that claims of a patent represent novel subject matter, the novelty of applicants' claims surely cannot be held out as a reason for asserting failure to meet enablement requirement.

The rejected claims are directed to the treatment of proliferative diseases by administering αβ-unsaturated sulfoxides according to Formula I. The compounds are cytotoxic to abnormally proliferating cells but not normally proliferating cells. The rejected claims are directed to treatment of proliferative diseases by administering the compounds to kill abnormally proliferating cells.

The nature of the invention claimed in the rejected claims is that the rejected claims are all directed to the treatment of diseases characterized by abnormal cell proliferation, particularly cancer. A common mechanism underlies all the diseases, namely abnormal cell proliferation.

The examiner did not make a finding concerning the level of skill in the art. However, applicants suggest that the level of skill is very high. The persons skilled in the art will typically be Ph.D. scientists specializing in drug discovery and development and/or medical doctors specializing in cancer treatment therapies. Those persons will be capable of designing and performing highly sophisticated experiments.

With regard to the state of the art and level of predictability, the art is not as unpredictable the examiner appears to believe. For example, researchers have identified the cell cycle as being crucial in diseases involving abnormal cell proliferation, such as cancer, making it credible that agents that intervene appropriately in the cell cycle could "halt[a] cancer cell in its tracks". See K. Collins, *et al., Proc. Nat. Acad. Sci. USA*, **1997**, *94*, 2776-78, a copy of which is provided herewith. Consistent with this, such anticancer drugs as are available tend to be effective against a broad range of cancers. The applicants provide herewith drug data sheets for some of the commonly used anticancer drugs, cisplatin, doxorubicin, and paclitaxel obtained from the Cancer Care Ontario website (http://www.cancercare.on.ca/index_drugFormulary.htm). Each drug is shown as being effective versus a range of cancers. For example, cisplatin has established utility versus at least the following cancers: bladder cancer, ovarian cancer, testicular

cancer, brain tumors, cervical cancer, germ cell tumors, head and neck cancer, both small cell and non-small cell lung cancers, neuroblastoma, osterosarcoma, esophageal cancer, Wilm's tumor, adrenocortical cancer, breast cancer, endometrial cancer, gastrointestinal cancer, gynecological sarcoma, hapatoblastoma, malignant melanoma, non-Hodgkin's lymphoma and thyroid cancer. Although the documents supplied are the current versions of the documents, it is respectfully submitted that since these drugs are well-established cancer drugs that the information can be taken as reflecting approximately the same state of the art as existed at the time of filing of the present application.

The examiner characterizes the state of the art as speculative. However, as demonstrated above, several broadly useful anticancer treatments are available. Such unpredictability as exists in the treatment of cancer can be largely explained due to the nature of the disease, particularly the variability in individual cancers and factors such as variability in the aggressiveness of the cancer, metastasis, and development of drug resistance. While these factors make response in between individuals variable and somewhat unpredictable, they do not detract from the general usefulness of a given drug.

In addition, with regard to the state of the art, routine *in vitro* screening methods are available to discover drugs that are effective in the treatment of proliferative disorders. For example, the applicants cite and provide data for *in vitro* cytotoxicity assays versus cancer cell lines. Such screening assays have been shown to correlate with *in vitro* activity and clinical effectiveness of cancer drugs. Rose, *et al.*, showed a significant correlation between *in vitro* and *in vivo* assays when fermentation extracts evaluated in an *in vitro* cytotoxicity assay against several tumor cell lines and then tested *in vivo* against P388 leukemia or B16 melanoma. W.C. Rose, *et al.*, "Correlation of in vitro cytotoxicity with preclinical in vivo antitumor activity", *Anticancer Res.*, **1988**, *8*(3), 355-67. Additional evidence of the predictiveness of *in vitro* cell line models was provided in a study by Voskoglou-Nomikos, *et al.* who showed that in vitro cytotoxicity results were predictive of efficacy observed in Phase II clinical trials in a study of thirty one anti-cancer compounds. T. Voskoglou-Nomikos, *et al.*, "Clinical Predictive Value of the in Vitro Cell Line, Human Xenograft, and Mouse Allograft Preclinical Cancer Models",

Clinical Cancer Res., **2003**, *9*, 4227-39. Copies of the Rose and Voskoglou-Nomikos references cited are supplied herewith.

The *in vitro* screening methods described in the preceding paragraph can be carried out routinely. One very prominent example of the routineness of assessment of new chemical entities for activity in proliferative disorders is the *In Vitro* Cell Line Screening Project (operated by the National Cancer Institute (NCI) of the National Institutes of Health for anticancer drug discovery. The NCI program has the capacity to screen 3,000 compounds per year against 60 different human tumor cell lines. A copy of a printout from the NCI website describing the program is provided herewith.

The applicants have provided considerable guidance and working examples for carrying out the invention, contrary to the examiner's assertion that no guidance has been provided. The specification provides detailed information defining the compounds of the invention as well as defining preferred embodiments of the compounds and describing methods of making the embodiments. Considerable guidance is also provided for the formulation and administration of the compounds as well as for administering the compounds and carrying out the claimed methods of the invention. For example, methods of screening for cytotoxic activity versus four cancer cell lines (Example 35) are described.

In view of the foregoing factors, the amount of experimentation required to practice the invention cannot be described as undue.

The compounds of the invention would be readily synthesized using conventional techniques for organic chemical synthesis.

The compounds of the invention could then be subjected to routine *in vitro* screening using the techniques described in the specification and otherwise known in the art. As the example of the NCI's screening program (with a capacity to test 3,000 compounds per year in 60 different cell lines) shows, such *in vitro* screens could be very routinely performed. As shown by the references cited by the applicants, such *in vitro* screens are predictive of *in vivo* activity.

Thus, the person skilled in the art would be able to select compounds for further evaluation by performing routine *in vitro* screening results that would be predictive of *in vivo* activity, and therefore results from the *in vitro* screening results could be used to predict which compounds would be most effective *in vivo*.

The *in vitro* screens can also be used to predict activity across a range of diseases. As shown above, anticancer drugs tend to be effective across a range of cancers, and thus, effectiveness of an agent in treating one proliferative disorder would be predictive of activity against another proliferative disorder. This arises because of the common mechanism - abnormal cell proliferation involving the cell cycle - involved in the different diseases. Even to the extent that activity is not consistent across different diseases, the person skilled in the art who wished to use the invention to treat a particular disease could readily implement a suitable *in vitro* screen by selecting a suitable cell line. The person skilled in the art would be able to choose a cell line characteristic of those which are proliferating abnormally in the particular disease condition from the very wide array of cell lines that are available. For example, data from cytotoxicity assays for four different cell lines, representing four different cancers are given in the specification in Example 35. However, the NCI screen uses at least 60 cell lines, and many further cell lines are described in the literature.

The applicants agree that clinical data would be required before a given compound would be able to be sold as a drug for the treatment of any particular disease (in order to satisfy regulatory requirements, for example), but the absence of such data from the specification or the need for experimentation to obtain such data are not inconsistent with satisfaction of the enablement requirement. The courts have recognized that the level of validation required for patentability is much lower than required, for example, to obtain F.D.A. approval to market a new drug. *See, e.g., In re Brana*, 51 F.3d, 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development."). The need for further experimentation is therefore fully consistent with the enablement requirement. *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988). The fact that the claims may encompass inoperative embodiments is

insufficient to show non-enablement, and the claims therefore need not exclude all inoperative embodiments. *See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, (Fed. Cir. 1984) (citing *In re Dinh-Nguyen*, 492 F.2d 856, 858-59 (C.C.P.A. 1974)).

In view of the complexity of developing the field of developing new pharmaceuticals, the quantity of experimentation required to practice the invention of the rejected claims cannot be described as undue. *Wands* recognized that the need for further experimentation is not inconsistent with enablement: "the key word is undue not experimentation". *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (quoting *In re Angstadt*, 537 F.2d 498, 504, 190 (C.C.P.A. 1976) (internal quotation marks omitted). Pharmaceutical drug discovery and development, and the treatment of cancer and other proliferative disorders are complex, to be sure, but the law does not preclude inventions in complex fields from patent protection. It is recognized that the fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983)). Few fields of endeavor rival the complexity of developing pharmaceuticals. It is respectfully submitted that the fact of the very high cost associated with developing a new drug (estimated to be in the range from about $500 million to $2,000 million for each new chemical entity) is reflective of the fact that drug companies "typically engage in" a substantial amount of experimentation in the course of drug development. The amount of experimentation that would be required to practice the claimed invention would therefore not be "undue".

In view of the foregoing, reconsideration of the examiner's findings concerning enablement of claims 33-35, 37 and 38 is respectfully requested. It is respectfully submitted that upon such reconsideration, the examiner should conclude that the rejection for lack of enablement under 35 U.S.C. § 112 should be withdrawn.

2 Rejection of Claims 1-6, 8-13, 15, 16, 18, 19 and 77 under 35 U.S.C. § 102(b).

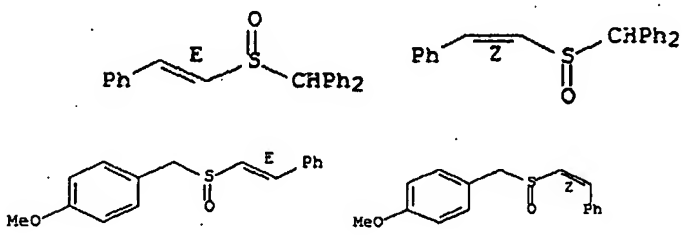
The examiner has rejected claims 1-6, 8-13, 15, 16, 18, 19 and 77 under 35 U.S.C. § 102(b) over several references as described below. Applicants respectfully request reconsideration in view of the amendments and comments herein.

The examiner has rejected claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly anticipated by Zhong, *et al.*, *J. Chem. Res. (Synop.)*, **2000**, 588-89 ("Zhong"). The applicants respectfully traverse.

The examiner states that Zhong discloses E-benzyl styryl sulfoxide. Although the examiner is correct that at least the abstract appears to disclose E-benzyl styryl sulfoxide, this disclosure would not have anticipated claim 1 or 3 because claim 1 had a proviso requiring at least one of A and B to be substituted when rings A and B were both phenyl. Claim 1 has been amended herein to delete "unsubstituted aryl" from the options for ring B (rendering the proviso unnecessary). Since the ring corresponding to ring B is an unsubstituted aryl group in the compounds described by Zhong, Zhong does not anticipate claim 1. The reference also does not anticipate claim 3 because claim 3 depends from claim 1.

The examiner has rejected claims 1-6, 8-13, 15, 16, 18, 19 and 77 under 35 U.S.C. § 102(b) as allegedly anticipated by Schwan, *et al.*, *J. Org. Chem.*, **1988**, *63*, 7825-32 ("Schwan"). Applicants respectfully request reconsideration.

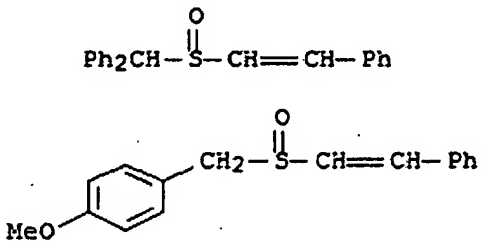
The examiner states that Schwan discloses the following compounds:



Claim 1 has been amended herein to delete "unsubstituted aryl" from the options for ring B. Since the ring corresponding to ring B is an unsubstituted aryl ring in all the above compounds described by Schwan, Schwan does not anticipate claim 1. Since claims 2-6, 8-13, 15, 16, 18, 19 and 77 all depend from claim 1, Schwan also does not anticipate these other rejected claims.

The examiner has rejected claims 1, 4, 5, 6, 8-11, 15, 18 and 77 under 35 U.S.C. § 102(b) as allegedly anticipated by Schwan, *et al.*, *Tetrahedron Lett.*, **1996**, *37*, 2345-48 ("Schwan 2"). Applicants respectfully request reconsideration.

The examiner states that the reference discloses the following compounds:



As explained above, claim 1 has been amended herein to delete "unsubstituted aryl" from the options for ring B. Since the ring corresponding to ring B is an unsubstituted ring in the compounds described by Schwan 2, Schwan 2 does not anticipate claim 1. Since claims 4, 5, 6, 8-11, 15, 18 and 77 all depend from claim 1, Schwan 2 also does not anticipate these other rejected claims.

Finally, the examiner rejected claims 1 and 2 under 35 U.S.C. 102(b) as being allegedly anticipated by Tanaka, *et al.*, *Nippon Kagaku Zasshi*, 1962, 895-901, which the examiner stated discloses Z-benzyl styryl sulfoxide. Applicants respectfully traverse.

Although the examiner is correct that at least the abstract of the reference appears to disclose Z-benzyl styryl sulfoxide, this disclosure would not have anticipated claim 1 or 2 because claim 1 had a proviso requiring at least one of A and B to be substituted when rings A and B were both phenyl. Claim 1 has been amended herein to delete "unsubstituted aryl" from

the options for ring B (rendering the proviso unnecessary). Since the ring corresponding to ring B is an unsubstituted ring in the compounds described by Tanaka, Tanaka does not anticipate claim 1. The reference also does not anticipate claim 2 because claim 2 depends from claim 1.

4. Response to the Claim Objections.

The examiner found that the subject matter of claims 7, 14, 17, 20-27, and 69 was allowable, but objected to these claims as being dependent from a rejected base claim.

The applicants respectfully submit that the response to the grounds of rejection set forth above overcomes the examiner's objection since the base claims have been placed in condition for allowance by the applicants' amendments.

Applicants also respectfully point out that in view of the fact that claim 69 was found allowable, and that claims 70 and 71 depend from claim 69 and are directed to the same chemical process, it should be especially clear that claims 70 and 71 should be rejoined and found allowable.

5. Conclusion.

Based on the foregoing, it is believed respectfully submitted that unity of invention has been established and that all claims are in condition for allowance. Applicants therefore respectfully request examination on the merits of all the claims presently pending, and respectfully solicit the issuance of a notice of allowance.

Respectfully submitted,

E. PREMKUMAR REDDY, *et al.*

BY 

DANIEL A. MONACO
Registration No. 30,480
Drinker Biddle & Reath LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Tel: (215) 988-3312
Fax: (215) 988-2757
Attorney for Applicants